2A (residues 35-64 of SEQ ID NO: 49), BMP-3 (residues 35-66 of SEQ ID NO: 50), BMP4 (residues 35-64 of SEQ ID NO: 51), BMP5 (residues 35-65 of SEQ ID NO: 52), BMP-6 (residues 35-65 of SEQ ID NO: 53), Dorsalin (residues 35-65 of SEQ ID NO: 54), OP-1 (residues 35-65 of SEQ ID NO: 55), OP-2 (residues 35-65 of SEQ ID NO: 56), OP-3 (residues 35-65 of SEQ ID NO: 57), GDF-1 (residues 35-70 of SEQ ID NO: 58), GDF-3 (residues 35-64 of SEQ ID NO: 59), GDF-9 (residues 35-65 of SEQ ID NO: 60), Inhibin α (residues 35-65 of SEQ ID NO: 61), Inhibin βA (residues 35-69 of SEQ ID NO: 62), Inhibin βB (residues 35-68 of SEQ ID NO: 63), CDMP-1/GDF-5 (residues 35-65 of SEQ ID NO: 83), GDF-7 (residues 35-65 of SEQ ID NO: 87), and a portion thereof.

5. (Twice amended) The chimeric protein of claim 1, wherein said finger 1 subdomain comprises the amino acid sequence of OP-1 (residues 2-29 of SEQ ID NO: 55), and said heel domain comprises a portion of the heel domain of OP-1 (residues 35-65 of SEQ ID NO: 55).

REMARKS

Applicants would like to draw the Examiner's attention to the fact that the correspondence address for the attorneys of record for this application is Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 and not Testa Hurwitz & Thibeault, LLP. In support of this, applicants submit herewith as Exhibit B a copy of the Reply to Notice to File Missing Parts including the Declaration and Power of Attorney for Patent Application filed in this application on March 10, 2000. Accordingly, applicants respectfully request that the Examiner forward all future correspondence to Fish & Neave.

Applicants acknowledge that the restriction

requirement mailed on February 14, 2000 (Paper No. 8) is reinstated.

In response to the Examiner's rejections and in order to expedite prosecution, applicants have canceled claim 7 without prejudice and without waiver of their right to file for and obtain claims directed to any non-elected subject matter in divisional and continuing applications which claim priority from this application.

Applicants have amended claims 1-3 and 5 to improve their form.

None of these amendments adds new matter.

Applicants now address the Examiner rejections.

THE REJECTIONS

35 U.S.C. § 112, second paragraph

Claims 1, 2, 5 and 6

The Examiner has maintained the rejection of claims 1, 2, 5 and 6 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner states that claims 1, 2, 5 and 6 are indefinite over the recitation of finger 1 and heel subdomains because it is unclear if finger 1 and heel domains are intended or if a subdomain of the finger 1 and heel domain are intended.

Applicants respectfully submit that claims 1, 2, 5 and 6 are clear. However, to expedite prosecution, applicants have amended claim 1 (and therefore, claims dependent thereon) to recite that the finger 1 subdomain comprises an amino acid sequence from a second, different member of said superfamily or a portion thereof and that the heel subdomain comprises an amino acid sequence from the second, different member of said superfamily or a portion

thereof.

Applicants have also amended claim 2 and 5 to recite the amino acid residues that define the finger 1 and heel subdomains of OP-1. Accordingly, applicants respectfully request that the Examiner withdraw this rejection.

35 U.S.C. § 103(a): Claims 1-3, 5 and 6

The Examiner has maintained the obviousness rejection of claims 1-3, 5 and 6 under 35 U.S.C. § 103. The Examiner contends that claims 1-3, 5 and 6 are unpatentable over Keck et al., U.S. patent 6,040,431 ("Keck") in view of Griffith et al., Proc. Natl. Acad. Sci, 93, pp. 878-883 (1996) ("Griffith"), Luyten et al., WO96/14335 ("Luyten"), Qian et al., Proc. Natl. Acad. Sci, 89, pp. 6290-6294 (1992) ("Qian") and Daopin et al., Science, 257, pp. 369-373 (1992) ("Daopin"). The Examiner states that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. The Examiner further states that Keck gives specific guidance as to the particular form of the claimed invention and how to achieve it and that Qian provides a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimeras because CDMP-2 has chondrogenic activity *in vivo* but substantially no osteogenic activity and an OP-1/CDMP-2 chimera would provide a practical approach to investigate structure/function relationships of chondrogenic versus osteogenic activity. The Examiner further argues that Daopin teaches a close structural similarity between TGF-β2 and BMP-2, and suggests that the only stable form of the TGF-β2 in solution is a dimer and that it would have been obvious to one of ordinary skill in the art at the time of the invention to make a dimer because of the close structural similarity between TGF-β2 and BMP-2 and the only

stable form of TGF-β2 is a dimer. Applicants traverse.

First, applicants respectfully submit that applicants did not argue that the claims of the instant application are non-obvious by addressing each reference separately. Rather applicants described the teachings of each reference and stated that nothing in the references either alone or in combination rendered the claims non-obvious.

Second, applicants maintain that the claims of the present application are non-obvious over Keck, in combination with Luyten, Griffith, Qian or Daopin.

Applicants respectfully submit that the Examiner's rejection amounts to no more than an "obvious to try" standard. The claims of the present application recite chimeric TGF-β superfamily member proteins comprising a dimer wherein one monomer comprises a CDMP-2 finger 2 subdomain and a finger 1 and heel subdomain from a second member of the superfamily. At the time of filing this application, it would not have been obvious to the skilled worker to swap the subdomains of a TGF-β superfamily member protein while maintaining biological activity. The finger 1, heel and finger 2 subdomains are tightly organized spatially such that the skilled worker would not expect a protein having its subdomains switched to maintain its biological activity. And, nothing in Keck in combination with Luyten, Griffith Qian or Daopin renders the claims of the present application obvious.

Keck discloses single chain analogs of the TGF-β superfamily wherein the analog comprises a finger 1, heel and finger 2 linked to each other via a linker. The single chain analogs disclosed in Keck comprise a finger 1, heel and finger 2 subdomain from the same member of the TGF-β superfamily and differ from the natural TGF-β superfamily members in that they are single chain proteins rather than

dimeric proteins. Moreover, the skilled worker reading Keck would expect that a linker would be necessary to link the three subdomains. Nothing in Keck teaches or suggests a dimeric or chimeric TGF-β superfamily member protein wherein one monomer comprises a CDMP-2 finger 2 subdomain and finger 1 and heel subdomains from a second member of the superfamily.

Luyten discloses the sequence of CDMP-2. Luyten does not identify the finger 1, heel and finger 2 subdomains of CDMP-2. Nor does Luyten teach or suggest chimeric proteins having enhanced properties such as folding, stability or solubility.

Griffith discloses the three dimensional structure of OP-1. Griffith also discloses that the TGF-β superfamily members are structurally similar. Griffith, does not teach or suggest chimeric molecules as claimed in the present application.

Qian discloses chimeras of TGF-β isoforms that share greater than 70% identity. Qian does not disclose or suggest chimeras of the members of the TGF-β superfamily of proteins. Moreover, Qian discloses a chimeric molecule of TGF-β1 and TGF-β2 comprising amino acids 1-39 of TGF-β2 linked to residues 40-82 of TGF-β1 linked to residues 83-122 of TGF-β2. Qian teaches a chimeric protein wherein the finger 1 and finger 2 subdomains are from the same member of the superfamily. Qian does not teach or suggest a chimeric molecule comprising a finger 2 domain of CDMP-2 and finger 1 and heel domains from a second member of the TGF-β superfamily as is recited in the claims of the instant application. Finally, nothing in Qian teaches or suggests a chimeric molecule comprising CDMP-2.

Daopin teaches the crystal structure of TGF-β2 and that TGF-β2 shares 66-80% identity with TGF-β1 through β5

and 25-40% sequence identity with other members of the superfamily. Daopin does not disclose or suggest the finger 1, heel and finger 2 subdomains of the members of the superfamily. Nor does Daopin disclose or suggest chimeric molecules comprising a finger 2 subdomain of CDMP-2 and a finger 1 and heel subdomain from a second member of the superfamily. In fact, nowhere in Daopin is there any mention of CDMP-2.

Applicants submit that there is no motivation to combine the teachings of Keck with those of any of Luyten, Griffith, Daopin and Qian. Keck merely discloses the domains of the TGF-β superfamily. Luyten and Griffith provide the crystal structures of OP-1 and CDMP-2, respectively. Daopin teaches that TGF-β1 -β5 shares 66-80% identity but that the identity with other members is much lower. Qian discloses a chimera between TGF-β1 and TGF-β2, which share 70% identity. None of these references provide the motivation to make the TGF-β superfamily member chimeras recited in the present application.

Moreover, even if the teachings of Keck were combined with those of Luyten, Griffith, Daopin and Qian, the combination of all of those references would not teach the claimed chimeric TGF-β superfamily proteins because none of the references suggests a chimeric molecule having a finger 1, heel and finger 2 subdomain that are not linked together by a linker. Nor would the skilled worker have a reasonable expectation of success that a chimeric molecule as claimed in the instant application would have enhanced properties such as folding, stability or solubility. Rather, the skilled worker would have expected that disruption of that spatial organization of the subdomains would disrupt the biological activity of the protein. In fact, Qian indicates this at page 6294 by stating "one could not be certain that

a chimeric TGF-β molecule would fold correctly". Therefore, the combination of references cited by the Examiner, at best provide an "obvious to try" situation, which is not the standard for obviousness.

For all the above reasons, applicants request that the Examiner withdraw the obviousness rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorney for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York, 10020-1104
Tel: (212) 596-9000

Appendix of Amendments

1. (Twice amended) A TGF-β superfamily chimeric protein, said chimeric protein comprising a dimer wherein one monomer comprises an amino acid sequence from [at least] two different members of said superfamily; wherein the monomer comprises a finger 1 subdomain, a finger 2 subdomain and a heel subdomain, wherein:

said finger 2 subdomain [being] consists of cDMP-2 (residues 68-98 of SEQ ID NO:86)[;] [,]

said finger 1 [or heel] subdomain comprises [comprising at least a portion of] [the] an amino acid sequence from [at least] a second, different member of said superfamily or a portion thereof;[,]

said heel subdomain comprises an amino acid sequence from the second, different member of said superfamily or a portion thereof; and

wherein said monomer further comprises a conserved C-terminal cysteine skeleton.

2. (Amended) The chimeric protein of claim 1, wherein the finger 1 subdomain comprises the amino acid sequence of [said second member is] OP-1 (residues 2-29 of SEQ ID NO: 55 [39]) or a portion thereof; and the heel subdomain comprises the amino acid sequence of OP-1 (residues 35-65 of SEQ ID NO: 55) or a portion thereof.

3. (Twice amended) The chimeric protein of claim 1, wherein:

the finger 1 subdomain comprises the amino acid sequence [said second member is] selected from the group consisting of TGF-β1 (residues 2-29 of SEQ ID NO: 40), TGF-β2 (residues 2-29 of SEQ ID NO: 41), TGF-β3 (residues 2-29 of SEQ ID NO: 42), TGF-β4 (residues 2 -29 of SEQ ID NO: 43), TGF-β5 (residues 2-29 of SEQ ID NO: 44), dpp

(residues 2-29 of SEQ ID NO: 45), Vg-1 (residues 2-29 of SEQ ID NO: 46), Vgr-1 (residues 2-29 of SEQ ID NO: 47), 60A (residues 2-29 of SEQ ID NO: 48), BMP-2A (residues 2-29 of SEQ ID NO: 49), BMP-3 (residues 2-29 of SEQ ID NO: 50), BMP4 (residues 2-29 of SEQ ID NO: 51), BMP5 (residues 2-29 of SEQ ID NO: 52), BMP-6 (residues 2-29 of SEQ ID NO: 53), Dorsalin (residues 2-29 of SEQ ID NO: 54), OP-1 (residues 2-29 of SEQ ID NO: 55), OP-2 (residues 2-29 of SEQ ID NO: 56), OP-3 (residues 2-29 of SEQ ID NO: 57), GDF-1 (residues 2-29 of SEQ ID NO: 58), GDF-3 (residues 2-29 of SEQ ID NO: 59), GDF-9 (residues 2-29 of SEQ ID NO: 60), Inhibin α (residues 2-29 of SEQ ID NO: 61), Inhibin βA (residues 2-29 of SEQ ID NO: 62), Inhibin βB (residues 2-29 of SEQ ID NO: 63), CDMP-1/GDF-5 (residues 2-29 of SEQ ID NO: 83), [and] GDF-7 (residues 2-29 of SEQ ID NO: 87), and a portion thereof; and

the heel subdomain comprises the amino acid sequence selected from the group consisting of TGF-β1 (residues 35-62 of SEQ ID NO: 40), TGF-β2 (residues 35-62 of SEQ ID NO: 41), TGF-β3 (residues 35-62 of SEQ ID NO: 42), TGF-β4 (residues 35-62 of SEQ ID NO: 43), TGF-β5 (residues 35-62 of SEQ ID NO: 44), dpp (residues 35-65 of SEQ ID NO: 45), Vg-1 (residues 35-65 of SEQ ID NO: 46), Vgr-1 (residues 35-65 of SEQ ID NO: 47), 60A (residues 35-65 of SEQ ID NO: 48), BMP-2A (residues 35-64 of SEQ ID NO: 49), BMP-3 (residues 35-66 of SEQ ID NO: 50), BMP4 (residues 35-64 of SEQ ID NO: 51), BMP5 (residues 35-65 of SEQ ID NO: 52), BMP-6 (residues 35-65 of SEQ ID NO: 53), Dorsalin (residues 35-65 of SEQ ID NO: 54), OP-1 (residues 35-65 of SEQ ID NO: 55), OP-2 (residues 35-65 of SEQ ID NO: 56), OP-3 (residues 35-65 of SEQ ID NO: 57), GDF-1 (residues 35-70 of SEQ ID NO: 58), GDF-3 (residues 35-64 of SEQ ID NO: 59), GDF-9 (residues 35-65 of SEQ ID NO: 60), Inhibin α (residues 35-65 of SEQ ID NO: 61), Inhibin βA (residues 35-69 of SEQ ID NO: 62), Inhibin βB (residues 35-68 of SEQ ID NO: 63), CDMP-1/GDF-5 (residues

35-65 of SEQ ID NO: 83), GDF-7 (residues 35-65 of SEQ ID NO: 87), and a portion thereof.

5. (Twice amended) The chimeric protein of claim 1, wherein said finger 1 subdomain [is] comprises the amino acid sequence of [from] OP-1 (residues 2-29 of SEQ ID NO: 55), and said heel domain comprises [at least] a portion of the heel domain of OP-1 (residues 35-65 of SEQ ID NO: 55).